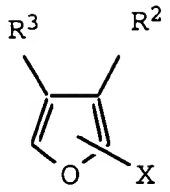


wherein X is [hydrogen or] hydroxyl;

wherein R^2 is aryl optionally substituted with a radical selected from halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, nitro, amino, sulfamyl and lower alkylsulfonylamino; and

wherein R^3 is aryl optionally substituted with a radical selected from halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, nitro, amino, lower alkylamino, lower alkylsulfonylamino and sulfamyl;

with the overall proviso [if when X is hydrogen then R^2 and R^3 are not both p-methoxyphenyl, p-chlorophenyl, p-bromophenyl, naphthyl and phenyl] **that one of R^2 and R^3 is phenyl substituted with methylsulfonyl or sulfamyl**; or a pharmaceutically-acceptable salt thereof.

REMARKS

Applicants appreciate the courteous interview granted to Applicants' attorney on April 12, 1997. Such interview was useful in advancing prosecution of this application.

The Office Action identified three rejections. Claims 47-52 and 55-60 were rejected under 35 USC §112, first paragraph, as not being enabled. Claims 47-50 and 55-58 were rejected under 35 USC §112, first paragraph, and under 35 USC §112, second paragraph, as not clearly describing the unconjugated furanone tautomeric form. Claims 47-50 and 55-58 were rejected under 35 USC §102(e) as being anticipated by Ducharme et al. Applicants respectfully request reconsideration and withdrawal

of these rejections in light of the following discussion.

I. The 35 USC §112, first paragraph rejection

Claims 47-52 and 55-60 were rejected under 35 USC §112, first paragraph, as not being enabled. Specifically, the Office Action states that the specification does not enable one of ordinary skill in the art to synthesize 2-hydroxyfurans. Applicants respectfully disagree.

Three references are cited in the Office Action (R. Elderfield, HETEROCYCLIC COMPOUNDS, Vol. 1, 177-89 (**1950**), A. Dunlop and F. Peters, THE FURANS, 170-74 (**1953**) and A. Hörnfeldt, Svensk kemisk tidskrift, 80, 343-57 (**1968**)) to support the proposition that hydroxyfurans are unstable, difficult to prepare and difficult to characterize. These "classic references" date from the 1950's and 1960's. Synthetic and analytical techniques have changed substantially since then.

a. Literature Support For Hydroxyfuran Preparation

Hydroxyfurans since have been described in the literature. For example, Rio and Serkiz (Bull. Soc. Chim. Franc., 1491-95 (1976), previously cited to the Patent Office, translation provided herewith) describe the preparation of 3,4-diphenyl-2-hydroxyfuric acid (Example 12a).

b. Affidavit Support For Hydroxyfuran Preparation

In view of the references describing hydroxyfurans and a knowledge of basic chemical mechanisms, one of ordinary skill in the art of heterocyclic chemistry would have known, at the time of filing the priority application (SN 08/004,822), that hydroxyfurans can be prepared from the intermediates and compounds identified in the application. The priority application describes mixed 3,4-diaryl-2,5-furyl carboxylic acid/esters in General Scheme 1 and in the accompanying text. One can prepare 3,4-substituted-5-hydroxyfuric acids (similar

to that described by Rio) from the mixed carboxylic acid/esters. Decarboxylation of the 5-hydroxyfuric acid, also described by Rio, proceeds through the 2-hydroxyfuran. This synthetic pathway is supported by the Declaration of Dr. Victor Snieckus (Appendix A), included herewith.

One of ordinary skill in the art of heterocyclic chemistry would have known, at the time of filing the priority application, that 3,4-diaryl-2-hydroxyfurans also can be prepared by other synthetic preparations, including via a furfural intermediate. Substituted furfurals can be prepared from either mixed 3,4-diaryl-2,5-furyl carboxylic acid/esters or 3,4-diarylfurans, both of which are described in the present application and the priority application. Oxidation of the furfural via the Baeyer-Villiger reaction proceeds through the 2-hydroxyfuran. This synthetic pathway is supported by the Declaration of Dr. Richard Silverman (Appendix B), included herewith.

c. Even Unstable Compounds Are Patentable

The Office Action implies that compounds need to be stable, easily synthesized and well characterized to be patentable. Applicants respectfully disagree.

The published Patent Office guidelines for enablement in chemical patent applications state:

> **"Naturally, for unstable and transitory chemical intermediates, the "how to make" requirement does not require that the applicant teach how to make the claimed product in stable, permanent or isolatable form."** USPTO Training Materials for Examining Patent Applications with Respect to 35 USC Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications (1996), citing *In re Breslow*, 205 USPQ 221, 226-7 (CCPA, 1980).

Patent law does not require that chemical compounds be isolated in a stable form so they can be bottled, or otherwise stored. The hydroxyfurans of the present invention need not be stable, easily synthesized or well characterized to be patentable.

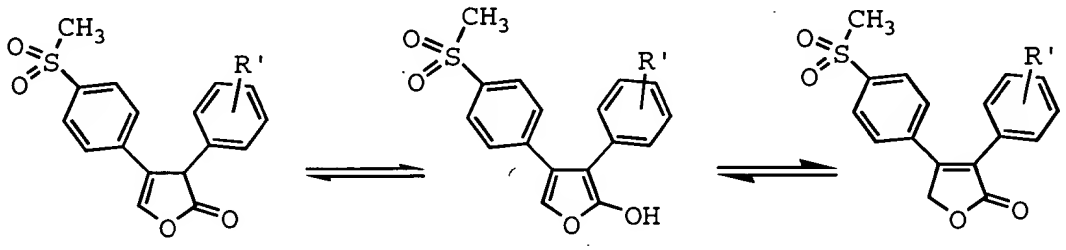
Accordingly, reconsideration and withdrawal of these rejections are respectfully solicited in view of the literature, the affidavits by Dr. Snieckus and Dr. Silverman, and the Patent Office's own guidelines.

* * * * * * * * * * *

The 35 USC §112, first and second paragraphs rejections

Claims 47-50 and 55-58 were rejected under 35 USC §112, first paragraph, and under 35 USC §112, second paragraph, as not clearly describing all the claimed furanone compounds. Applicants respectfully disagree.

The furanones and hydroxyfuran compounds of the current invention are merely tautomeric forms of each other (representative structures shown below).



carbonyl enol carbonyl

The following evidence supports the description and equality of these tautomeric forms.

a. One Of Ordinary Skill Recognizes Tautomer Equality

One skilled in the art knows a depiction of one tautomeric form embodies the other tautomeric forms. This position is supported with independent Declarations by Dr. Peter Beak

(Appendix C), Dr. Victor Snieckus (Appendix D) and Dr. Richard Silverman (Appendix E). Thus, the hydroxy-substituted furan also embodies the corresponding conjugated and unconjugated furanone tautomeric forms.

b. Analytical Evidence Of Tautomer Equilibrium

Corroborating evidence of the tautomeric equivalence of hydroxyfurans and furanones can be shown by modern analytical techniques. The equilibrium between the tautomeric hydroxy, unconjugated carbonyl and conjugated carbonyl forms has been observed by nuclear magnetic resonance (NMR) methods, as described in the Declaration of Dr. John Likos (Appendix F), included herewith. A substantial amount of the hydroxyfuran form is detected (up to 90% hydroxyfuran, depending on the aryl ring substitution) in base catalyzed tautomerization. NOE experiments indicate the tautomeric forms are in chemical exchange and interconverting with each other. Deuterium exchange reactions incorporate deuterium at position 5 of the furan ring, which is definitive proof that the hydroxyfuran is being formed.

This analysis of Dr. Likos is supported by the Declaration of Dr. Gideon Fraenkel (Appendix G), an independent expert in NMR analysis. Dr. Fraenkel reviewed the data and reached identical conclusions that

1) the three tautomeric forms have been detected, and
2) the tautomeric forms are in equilibrium with each other.

Dr. Fraenkel's Declaration is included herewith.

Thus, the NMR results clearly show the presence of, and the equilibrium between, the different forms of the compounds of the present invention. This correlates with what those skilled in the art know about such tautomeric forms.

Hydroxyfurans are described in the present application as being antiinflammatory agents (pages 4-8 of the present

application, pages 2-4 of the priority document). The furanones and hydroxyfuran compounds are tautomeric forms of each other. One tautomeric form depicts the other forms. Therefore, if one tautomeric form is described, all forms are described. Applicants believe that the speicification enables the hydroxyfurans and their tautomeric forms. Accordingly, reconsideration and withdrawal of these rejections are respectfully solicited.

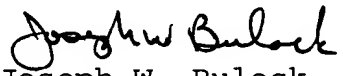
* * * * * * * * * * *

III. The 35 USC §102(e) rejection

Claims 47-50 and 55-58 were rejected under 35 USC §102(e) as being anticipated by Ducharme et al., U.S. Patent No. 5,474,995. The current Claims find support in the parent application, Serial No. 08/004,822, in Claim 1 and on pages 2-4. The parent application has a filing date of January 15, 1993, prior to the filing date of Ducharme. Therefore, Ducharme is not prior art against the present claims. Withdrawal of the 102(e) rejection is respectfully requested.

It is therefore respectfully submitted that Claims 49, 51, 57 and 59 are now in condition for allowance. Accordingly, reconsideration and withdrawal of the outstanding rejections, and allowance of Claims 49, 51, 57 and 59 are respectfully solicited.

Respectfully submitted,



Joseph W. Bulock
Attorney for Applicants
Registration No. 37,103
(314) 694-9094

G.D. Searle & Co.
Corporate Patent Office
P.O. Box 5110
Chicago, IL 60680-9889